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Title: Development of a Chemotherapy Regimen Interaction Database for the Mobile Internet:
Detecting Interactions with Psychotropics through OncoRx-MI

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ABSTRACT

Introduction: Cancer patients are at high risks of manifesting drug-drug interactions (DDIs). Clinicians need to know the magnitude of DDIs so as to better manage their patients' drug therapies. We have previously created a novel interaction database for oncology prescriptions (OncoRx). In this project, we leverage on 3G networks to further develop this database into an iPhone-specific application for the Mobile Internet (*OncoRx-MI*).

Methodology: Data on anticancer drugs (ACDs), chemotherapy regimens (CRegs) and DDIs with psychotropics were compiled from various hardcopy and online resources, and published articles from PubMed, Scopus and Science Direct. The database and iPhone web documents were designed using Adobe Dreamweaver CS4 and associated with a combination of open-source programming scripts.

Results: OncoRx-MI currently detects over 5000 DDIs (69.3% pharmacokinetic, 30.7% pharmacodynamic) between 256 single-agent and combination CRegs with 51 psychotropic drugs. OncoRx-MI fits the iPhone screen configuration, and displays information regarding the regimen, pharmacokinetics of the drugs, and detected DDIs in tabular format for improved usability.

Conclusion: OncoRx-MI is the first mobile DDI application of its kind which detects interactions for combination CRegs. It is aimed to help clinicians improve the pharmaceutical care of cancer patients through the management of DDIs in the clinical setting.

INTRODUCTION

Anticancer therapy generally involves the use of chemotherapy regimens comprising of either a single-drug or multiple drugs, so as to maximize therapeutic outcomes. Newer drugs, such as the targeted therapies, are gaining widespread interests in the treatment of cancer [1-4], and are also considerably being used in combination with first-line cytotoxic chemotherapies [5]. However, the increase in the use of combination therapies in cancer patients poses them to high risks of manifesting drug-drug interactions (DDIs) [6,7]. This is because anticancer drugs (ACDs) not only have complex pharmacological profiles, but also narrow therapeutic indices and steep dose-toxicity curves. In addition, physiological changes which occur in cancer patients predispose them to high incidences of DDI-related adverse events such as alterations in their pharmacokinetics and pharmacodynamics [8,9]. This poses a potential problem in clinical practice due to the serious and life-threatening clinical events that might occur. Failure to recognize these harmful DDIs may give rise to negative outcomes in patients. Clinicians must be vigilant when prescribing other concomitant medications with ACDs so as to prevent unwanted toxicities and inadequate drug exposures due to DDIs. Pharmacokinetic and/or pharmacodynamic interactions can lead to clinically significant toxicities or therapeutic failures [6]. Thus, it is essential that they know the magnitude of the DDIs so as to better manage their patients' drug therapies.

Information and internet technologies have gained increasing acceptance among healthcare professionals in their clinical practice. The emergence of the World Wide Web (WWW) has impacted the way in which health-related information is distributed and accessed over cyberspace. The convergence of information platforms has also enabled the use of internet-enabled mobile phones which implies a greater possibility of web access [10]. Newer handheld

technologies, increasing support for hypertext and multimedia applications, and a variety of inexpensive browsers have paved more alleys for health- and drug-related information to reach the public in a convenient and hassle free manner. Healthcare professionals can now keep themselves updated in the latest developments in oncology, and also proper therapeutic management strategies through the use of online databases and software tools [11].

Drug information databases which provide relevant DDI information on ACD therapies can potentially improve pharmaceutical care in cancer patients and improve their quality of life. There are many online databases which are available as drug information resources to healthcare professionals [12-15]. Advancement in technology has also encouraged the use of personal digital assistants (PDAs) by many healthcare professionals in their place of work, and some resources (e.g. Epocrates) offer downloadable PDA versions for convenient use as well. While these technological tools have positively influenced many aspects of patient care such as medication prescribing and disease-state management, it has been suggested that information obtained from online databases may be prone to errors which may impact patient safety and efficacy [16]. Furthermore, the information from downloadable versions of such drug information databases also tends to be less comprehensive in terms of scope and completeness [17,18].

The advent of 3G (3rd Generation) networks has allowed its users to surf the WWW at faster speeds and higher data rates [19]. With the launch of the Apple's iPhone (3G version), many healthcare professionals have also caught on its popularity and cultural status [20]. Thus, many iPhone-specific medical applications (e.g. Epocrates Rx, AirStrip OB and Drugs.com) have also emerged in response to this demand [20]. However, currently there is no drug interaction database dedicated to allow the search of ACD interactions by combination chemotherapy regimens. Most of the currently available DDI databases require the input of individual drugs in a

patient's prescription in order to search for ACD interactions. We have previously created an oncology-specific interaction database for oncology prescriptions (OncoRx) on the WWW [21,22]. Leveraging on the advantages of 3G networks, the objectives of this project are two-fold: (a) to further develop of this database to include an iPhone-specific web-based application as a starting point for mobile devices, and (b) to ensure that no loss of DDI content occurs between the online and mobile versions of the database. This paper describes the development of the iPhone application called "*OncoRx-MI*" for the mobile internet.

METHODOLOGY

The development of OncoRx-MI involves the collation and compilation of drug-related information from published literature sources, and the creation of the iPhone application. A summary of the development process is shown in **Figure 1**.

Collation and Compilation of Drug-related Information

Drug information on ACDs and DDIs were collated and compiled from the various hardcopy resources [23-28], online databases [29-33] and drug interaction checkers [34-41]. In addition, information was obtained from the package inserts of each drug, and literature searches were carried out in PubMed, Scopus and Science Direct regarding ACD interactions with central nervous system (CNS)-acting drugs (also known as psychotropic drugs). Single-agent and multiple-agent chemotherapy regimens that were positively evaluated in Phase II or III trials and published in English-language journals, or regimens approved by the US Food and Drug Administration (FDA), were also compiled together with substantiating references in scientific

literature, and each individual ACD used in the chemotherapy regimen would then be listed out so that its interactions with the psychotropics could be identified.

Compiled drug-related information included the generic names of the ACDs and psychotropics, their pharmacological categories, mechanisms of action and pharmacokinetic properties. Chemotherapy-related information included the acronyms of the chemotherapy regimens, drugs used in the regimen, the types of cancers they treat, and substantiating references. Interaction-related information consisted of the interaction effects, mechanisms of interaction, substantiating evidences and references, and proposed management plans. DDI literature collated included in-vitro studies, animal models, human case reports, clinical studies, and other relevant abstracts and review articles that were published in English.

Creation of the iPhone Application

The compiled data was distributed into interrelated tables in Microsoft Excel and stored in a Structured Query Language (MySQL 5.0) database. The iPhone web documents were created using the Adobe Dreamweaver CS4, and associated with a combination of hypertext markup languages (HTML) and javascripts. Cascading style sheets (CSS) were used to provide a consistent look for the web documents.

The OncoRx-MI database was programmed with hypertext preprocessor (PHP5) scripting, and the web documents were then uploaded onto a domain bought from an internet web hosting company [42]. Although other scripting languages such as Active Server Pages (ASP) and Perl could also be used, PHP was employed because of its ease of implementation and ability to integrate with the other programming languages used in this project.

RESULTS

OncoRx-MI is an oncology-specific database that is able to identify interactions with ACDs and combination chemotherapy regimens. This database can be accessed through the iPhone Safari browser at <http://www.onco-informatics.com/OncoRxMI/>. The module described in this study concentrates on interactions of ACDs, as well as single- and multiple-agent chemotherapy regimens with psychotropic drugs.

Database Statistics

The OncoRx-MI application is currently capable of detecting over 5000 DDIs between 256 single-agent and combination chemotherapy regimens with 51 psychotropic drugs. **Table I** shows the list of chemotherapy regimens and psychotropic drugs that can be detected by the OncoRx-MI database. These include the anticonvulsants, antidepressants, central nervous system (CNS) stimulants, drugs for attention-deficit hyperactive disorder (ADHD) and substance-dependence agents.

The DDIs detected were focused primarily on pharmacokinetic (69.3%) and pharmacodynamic (30.7%) mechanisms (**Table II**). Regimens for lymphomas and myelomas had the highest proportions of pharmacokinetic (18.2%) and pharmacodynamic interactions (10.4%), which made up over a quarter of the total DDIs (28.6%). In contrast, the lowest proportion of total DDIs was observed for regimens indicated for gastrointestinal, colorectal, liver and pancreatic cancers (5.5%). This could have resulted from low proportions of pharmacokinetic (4.3%) and pharmacodynamic (1.2%) DDIs observed for this category of regimens. When compared with regimens for other types of cancers, this group had the lowest proportion of

pharmacokinetic DDIs. However, there was another group of chemotherapy regimens that had an even lower proportion of pharmacodynamic DDIs (1.0%) – those for the treatment of lung cancers. Majority of the pharmacokinetic interactions involved the induction (49.5%) and inhibition (28.8%) of the cytochrome P450 isozymes (e.g. CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4), while the 3 most prominent pharmacodynamic interactions involved increased risks of cardiotoxicity, QT prolongation and torsade de pointes (31.0%), hepatotoxicity (23.1%), and neurotoxicity and peripheral neuropathy (15.3%).

Application Interface for Clinician Users

Clinician users can search for drug interactions from 2 search interfaces – either generic names of the ACDs or chemotherapy regimens based on its acronym. As an example, a DDI search between fluoxetine (an antidepressant) and the chemotherapy regimen FEC, consisting of cyclophosphamide, epirubicin and fluorouracil, used for the treatment of breast cancer [43,44], is shown (**Figure 2**).

When the clinician logs into the application, he can select the drugs and/or chemotherapy regimen from the iPhone dropdown menu. The relevant results will then be presented to the user in tabular format. The tables are designed to fit into the screen size of 320x480 pixels, and the words are shown in an easily readable format for users so that they do not need to zoom in using his fingers to enlarge the words. Furthermore, the web pages follow a longitudinal format so that the user scrolls in an up-down fashion instead of sideways.

On the results page, users are shown their choice of ACD or chemotherapy regimen and the psychotropic drug, followed by 4 links which they can tap to bring them to the relevant information – data on the chemotherapy regimen, pharmacokinetic parameters of the ACDs in the

regimen and the CNS-acting drug, as well as the detected DDIs (**Figure 3**). Pharmacokinetic information include the absorption, metabolism and elimination routes of the drugs, as well as enzymatic parameters. In addition, if a chemotherapy regimen is selected, information regarding the regimen will also be displayed to the clinician. These include the acronym and type of regimen, the type of cancer it treats, drugs in the regimen, as well as relevant citations. The DDI parameters that are provided include the interaction effects and mechanisms, an evidence summary, as well as a management plan. Alternative psychotropics belonging to the same pharmacological category in which no DDIs can be detected by the database will also be shown.

Since clinician users are critical to the success of OncoRx-MI, two additional features which cater towards its usability were also developed for those who are also iPhone users. In order to cater for easy access to OncoRx-MI, a web clip icon was created so that they could store the shortcut on their iPhone's home screen (**Figure 4**). This makes it easier for oncology clinicians who are on-the-go and need to access DDI information in their practice. Furthermore, an online form was also included so that they could feedback about their experiences with OncoRx-MI, and help improve the database or interface design.

DISCUSSION

As far as we know, there is currently no mobile oncology-specific database that allows for DDI searches by both individual ACDs and chemotherapy regimens. OncoRx-MI, where “OncoRx” refers to oncology drug and/or chemotherapy regimen prescriptions and “MI” stands for the *Mobile Internet*, is the first application of its kind where practitioners can search for DDIs of chemotherapy regimens on the mobile web. OncoRx-MI not only saves time and effort on the part of healthcare professionals in searching for chemotherapy drug interactions “on-the-spot”

when they encounter such DDIs in their practice, but is also practical since patients with cancer are often on combination regimens in which the individual drugs within the regimen are usually standard. As a first of its kind, OncoRx-MI also offers a proposed plan for the overall management of the patient on that particular regimen. In addition, the drug information in OncoRx-MI is summarized and placed under appropriate headings so that healthcare practitioners can rapidly sieve out the information they need. They can then get an overall view of the interactions in the regimen instead of collating and extracting relevant information for each individual drug by themselves.

Clinical Relevance and Designing for Pharmaceutical Applications

Although drug information databases catering towards DDIs are not new, and many have caught on the trend of designing applications for handheld devices such as PDAs and mobile phones, creating and designing a mobile application for interactions of chemotherapy regimens can be a challenging process. Some chemotherapy regimens may consist of multiple ACDS (e.g. BEACOPP consists of 7 drugs – bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone [45]), and it is not only time-consuming for oncology clinicians to search for DDIs of each individual ACD within the regimen, but also inconvenient in practice due to the time constraints in clinic visits. If they are in a rush for time, searching for multiple drug-pair interactions in a combination regimen may predispose them to a risk of accidental omissions of a DDI search with a particular ACD within the regimen, which may lead to a possibility of drug-related problems and adverse outcomes in patients. Furthermore, the content in handheld downloadable versions of drug information databases may compromise in terms of scope and completeness [17,18].

We have previously identified the pharmaco-cybernetic maxims for designing pharmaceutical tools [46], and we encourage designers of mobile drug-based applications to apply these maxims in their application tools as well. In particular, the content provided by such applications should follow 4 basic principles: it should be (a) accurate and of good quality, (b) of sufficient quantity to enable the healthcare professional or patient make a well-informed decision, (c) relevant to what the clinician or patient needs to know, and (d) clearly conveyed to its target audience.

OncoRx-MI was created with oncology healthcare professionals in mind as its target audience, but it is also useful for practitioners who have just graduated or from other clinical specialties, and are new to the oncology scene, thus they may not be familiar with anticancer drug and/or chemotherapy regimen interactions. The application is different from its online parent version (called OncoRx) on the WWW, in which the interface is catered for a larger screen size and resolution for use on computers (desktops, laptops and netbooks) (**Figure 5**). Studies have suggested that healthcare practitioners, particularly in hospital settings, experience certain environmental barriers to accessing online drug information [47]. Among them are issues related to restricted access to the internet/intranet in clinical areas, connection or firewalls which impede access, and a limited number of computers, or slow and old computers in wards or treatment areas. It has also been suggested that practitioners may prefer programs with alternative versions for handheld devices [48]. Hence, efforts have been made in this project to shrink the screen resolution down to one that is suitable for the mobile web, yet not compromise in terms of content. By leveraging on the use of 3G networks which are already available on most internet-enabled mobile devices, the DDI content provided to clinicians in both its mobile and online versions are exactly the same, since both versions draw the drug- and interaction-related

information from the same SQL database. Hence, the quality of information provided by the mobile application is not compromised when compared to its parent version.

A previous study done by our group had suggested that healthcare professionals deemed certain interaction parameters (e.g. interaction mechanisms, severities and risks, presence of management plans and non-interacting alternatives) to be more essential than others in terms of clinical relevance [48]. OncoRx-MI provides these parameters on top of other drug- and chemotherapy-related information, such as the pharmacokinetics of the interacting drugs, and a summary of the interaction evidence. Furthermore, as the information in the database is derived from a variety of hardcopy and online resources, this not only makes the OncoRx-MI application a comprehensive one, but it can also detect any discrepancies that exists for a particular drug interaction, so that clinicians can make a well-informed decision with regards to the therapies of their patients.

Limitations and Future Work

A main limitation of this database is its ability to only detect interactions with certain categories of psychotropic agents. However, since our database is updated in modular format, other modules on DDIs with other classes of drugs (e.g. agents for cardiovascular diseases) are currently underway. In addition, OncoRx-MI does not include the doses and frequencies of the chemotherapy regimens and psychotropic therapies as part of its results to clinician users. This is intended in future when its pool of users expands and clinicians from specializations other than oncology frequent this mobile web application.

In terms of the user interface, the links provided by OncoRx-MI can be small and difficult for users to tap or “click” with their fingers. This is because the original database was designed

with mouse-clicks in mind. The interface has also not tested on other handheld devices other than the iPhone, and hence technical disparities with the screen resolution and interface designs may differ when viewed with other mobile devices. Further development is underway to improve its search interface for use in other types of mobile devices (e.g. android phones) so that it can reach a wider target audience of healthcare professionals. Nevertheless, OncoRx-MI is still useful since it is able to identify a substantial number of interactions with single-agent and combination regimens used in clinical practice in its current stage.

OncoRx-MI is a unique application in that it was not developed by multidisciplinary teams of healthcare professionals and informatics experts from commercial organizations. Instead, it was created by a PhD candidate with a background in pharmacy and dual-trained in digital media creation, as part of a doctoral research project, in consultation with professors who are registered pharmacists in the Pharmacy Department at the National University of Singapore, one of whom is also US board-certified in oncology and pharmacotherapy. Hence, there is a limitation in manpower in terms of the frequency of updates to the database. As such, it is intended that the OncoRx-MI database and application be updated on an annual basis once it is able to detect a substantial amount of DDIs with other categories of drugs. The content provided by this application is dynamic and we are definitely receptive of any feedback provided by clinician users so that the application can be clinically useful and relevant to their practices.

CONCLUSION

OncoRx-MI is a mobile web application which allows the identification of DDIs between chemotherapy regimens and adjuvant drug therapy. This tool is the first of its kind to be able to identify interactions with both single-agent and combination regimens, and is able to provide

clinician iPhone users with clinically-relevant DDI information. We hope that OncoRx-MI will complement the currently available drug database applications developed for handheld devices so as to increase the awareness of oncology drug interactions among healthcare professionals, and ultimately improve the pharmaceutical care of patients with cancer.

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DECLARATION OF INTEREST

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